REMARKS/ARGUMENTS

Upon entry of the present amendment, claims 1, 3-8 and 10-27 will be pending in the above-referenced patent application and are currently under examination. Claim 1 has been amended. No new matter has been introduced with the foregoing amendment. Reconsideration is respectfully requested.

FORMALITIES

Support for the amendment is found throughout the application as originally filed. Applicants have amended claim 1 to delete the phrase "but still retains the shape of the compression-coated solid composition to a certain extent although it is being eroded," thus making the claim clearer by removing the relative language. As such, Applicants respectfully request that the Examiner enter the amendment.

As noted in Applicants response of February 24, 2004, Applicants previously submitted an Information Disclosure Statement on December 10, 2002. To date, Applicants have not received an initialed copy of Form PTO/SB/08B evidencing that the Examiner reviewed the same. Applicants respectfully request that the Examiner initial a copy of the previously submitted IDS and return the same to the undersigned representative.

THE INVENTION: TIME-RELEASE TABLET HAVING A SOLUTION CENTER

The present invention relates to a timed-release compression-coated formulation. The timed-release of the present invention is achieved by the specific formulation of the core tablet and outer layer. The core comprises an active ingredient and a freely erodible filler, and the outer layer comprises a hydrogel-forming polymer substance and hydrophilic base. As the tablet traverses the water rich upper digestive tract, the hydrophilic base in the outer layer absorbs water. This water is retained by the formation of a hydrogel. As the tablet continues along the digestive tract, the outer layer dissolves while the water that has been retained penetrates into the core of the tablet and begins eroding the filler to make a core that is part solid

filler and drug, and part solution containing filler and drug. The core that is part solution remains trapped in the tablet as a result of the outer layer that has not yet dissolved sufficiently to release the core. After the core has eroded from approximately 40% to approximately 90%, the outer layer dissolves to a sufficient degree that the core that is now substantially solution, is released into the lower digestive tract. The presence of the water that has been retained by the core allows for rapid uptake of the drug.

REJECTION UNDER 35 U.S.C. § 112, ¶ 2

Claims 1 and 3-24 were rejected under 35 U.S.C. § 112, ¶ 2 as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The Examiner alleges that the term "to a certain extent" is a relative term, rendering the claim indefinite. Applicants respectfully note that claim 1 has been amended to remove the allegedly relative term. Accordingly, Applicants respectfully note that the rejection is now moot.

REJECTION UNDER 35 U.S.C.§ 103

Claims 1, 3-8 and 11-27 were rejected as allegedly being obvious over the combined disclosures of Dandiker *et al.*, (U.S. Patent No. 5,425,950), Nakashima *et al.* (EP 0 661 045), Taniguchi *et al.* (EP 0 709 386), Wong *et al.* (U.S. Patent No. 5,391,381) and Kawata *et al.* (U.S. Patent No. 4,404,183). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

As set forth in M.P.E.P. § 2143:

> [t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure.

In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)

Applicants assert that a *prima facie* case of obviousness has not been established as there is no suggestion or motivation to modify the cited references.

A. There is no suggestion or motivation to modify the references

Applicants state that there is simply no motivation or suggestion provided in the cited references to modify their teaching in the way the Office Action has contemplated. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

1. Dandiker *et al.*

Dandiker *et al.* disclose a compression coated tablet having an inner layer comprising a drug and a filler, and an outer layer comprising a pH independent hydrophilic polymer in combination with a filler. While the outer layer of Dandiker *et al.* appears to operate to transport the core of the tablet of Dandiker *et al.* to the lower digestive tract, the core of Dandiker *et al.* does not begin to erode **until** the outer layer is completely dissolved and the core is exposed to the environment of the lower digestive tract. In fact, Dandiker *et al.* specifically states that it is the object of the invention that **the core NOT erode until the outer layer has dissolved**, col. 5, lines 24-29:

> It will be appreciated that the rapidly disintegrating inner layer or layers in the compositions according to the invention will only **start to disintegrate once the outer pH independent hydrophilic polymer layer has been removed** to expose a portion or all of the inner layer. (emphasis added)

Accordingly, the filler of Dandiker *et al.* must be different than the filler of the present invention since the filler of Dandiker *et al.* does not dissolve until after removal of the outer layer, while the filler of the present invention substantially dissolves prior to removal of the outer layer.

M.P.E.P. § 2141.02 requires that the invention as a whole be considered, "including portions that would lead **away from** the claimed invention." (emphasis added) Accordingly, the present invention cannot be taught by Dandiker *et al.* since the core does NOT erode prior to removal of the outer layer.

As the Examiner notes, "[a]ny known filler will erode 40-90% in the digestive tract given enough time." While this may be true[1], Applicants note that the filler of the present invention erodes while **encapsulated by the outer layer**, prior to exposure to the environment of the lower digestive tract. In stark contrast, the core of Dandiker *et al.* erodes only **after** exposure to the environment of the lower digestive tract. Accordingly, Dandiker *et al.* provides no suggestion or motivation to make the present invention.

2. Nakashima *et al.*

Nakashima *et al.* do not supply the deficiencies of Dandiker *et al.* In contrast to the present invention, Nakashima *et al.* disclose a *sustained release formulation* that comprises a tablet containing a *single layer* comprising a drug, a hydrophilic base, and a hydrogel-forming polymer. Accordingly, as the Nakashima *et al.* tablet travels through the digestive system, the tablet is continuously eroded, thereby releasing drug at every step along the way, from the upper digestive tract to the colon.

However, Nakashima *et al.* do not teach or suggest a multi-layer tablet that comprises a core that erodes while protected by a hydrogel outer layer such that when the core is exposed to the lower digestive tract environment, the core is in substantially a solution state. Accordingly, Nakashima *et al.* provides no suggestion or motivation to make the present invention.

3. Combination of Dandiker *et al.* and Nakashima *et al.*

The Examiner suggests that the coating of Nakashima *et al.* "is optimal for a timed-release delivery in the digestive tract, since the coating is formulated to allow the center to erode slowly as the unit passes over through [*sic*] the GI tract." However, as the data in Table 3

[1] Applicants do not acquiesce on this issue.

of the accompanying declaration by Dr. Hiromu Kondo shows, (Kondo declaration, explained in detail below) a formulation using an outer layer of Nakashima *et al.* in combination with the core of Dandiker *et al.* demonstrates at most a 4.3% erosion (Formulation 3, Table 3, page 4 of the Kondo declaration). In stark contrast, the present invention demonstrates erosion of approximately 40% to approximately 90% (*e.g.*, 84.1%) (Table 5, page 5 of the Kondo declaration). Clearly, the addition of filler in the core of the instant invention allows substantial core erosion to a solution state prior to exposure to the lower digestive tract environment.

The table below compares the key features of the instant invention, Dandiker *et al.* and Nakashima *et al.* As can be seen, the instant invention has several features in common with each of Dandiker *et al.* and Nakashima *et al.*, but operates via an entirely different methodology. While Dandiker *et al.* teaches a tablet where the core erodes after removal of the outer layer, and Nakashima *et al.* has no core layer, the instant invention teaches a tablet where the core erodes prior to removal of the outer layer.

	Instant invention	**Dandiker *et al.***	**Nakashima *et al.***
Outer layer composition	• hydrophilic base • hydrogel forming polymer	• pH independent hydrophilic polymer • filler	• hydrophilic polymer • hydrogel forming polymer • drug
Core composition	• drug • filler	• drug • filler	
Timing for core erosion in relation to removal of outer layer	BEFORE	AFTER	n/a
State of core upon removal of outer layer	Substantially solution	Solid	n/a

Accordingly, the combination of Dandiker *et al.* nor Nakashima *et al.* does not teach or suggest a multi-layer tablet having a substantially solution core for quick-release of a drug. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

4. Taniguchi *et al.*, Wong *et al.* and Kawata *et al.*

Taniguchi *et al.*, Wong *et al.* and Kawata *et al.* do not teach or suggest a multi-layer tablet where the core substantially erodes to form a solution state prior to dissolution of the outer layer. Accordingly, there is no suggestion or motivation to combine with Dandiker *et al.* and Nakashima *et al.* to make the present invention. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

OBJECTIVE EVIDENCE REBUTS ANY PRIMA FACIE CASE OF OBVIOUSNESS

Applicants can rebut a *prima facie* case of obviousness by presenting comparative test data showing that the claimed invention possesses unexpectedly improved properties or properties that the prior art does not possess. *In re Dillion*, 16 U.S.P.Q. 1897, 1901 (Fed. Cir. 1990). Applicants maintain that a *prima facie* case of obviousness has not been established. However, the comparative data filed in the accompanying Kondo declaration contains objective evidence which rebuts any *prima facie* case of obviousness.

In paragraphs 4-5, Dr. Kondo generally explains the invention. As explained therein, in order to accomplish the collection and retention of water, as well as the fast delivery of the drug in the lower digestive tract, the present invention consists of a tablet having at least two layers. The outer layer consists of a hydrogel forming polymer and a hydrophilic base (see Exhibit 2). The hydrophilic base acts to absorb water when the tablet is in the upper digestive tract, and the hydrogel forming polymer forms a hydrogel that retains the water as the tablet enters the lower digestive tract. The inner layer comprises a drug and a filler that erodes on contact with water (see Exhibit 2).

Further, as the hydrophilic base of the outer layer absorbs water, a hydrogel forms in order to retain the water, and the water in the tablet penetrates into the inner layer eroding the erodible filler such that the inner layer substantially becomes a solution state or suspension state. The result is that as the tablet moves from the upper to the lower digestive tract, the tablet has an outer layer that is slowly dissolving, but substantially retaining water, and the inner layer is

substantially liquid (see Exhibit 3). The advantage of having a substantially liquid inner layer is that when the outer layer is finally peeled away, the inner layer does not then have to dissolve in order to enable absorption of the drug. When the outer layer completely or partially dissolves, the inner layer is already substantially dissolved and enables rapid absorption of the drug, even in the lower GI tract where there is little water.

As Dr. Kondo declares in paragraph 6, a comparison of the percent erosion and the area under the plasma concentration curve (AUC) data from Example 9 (inventive) and Comparative Example 1 of the present invention (Table 1, below, see also page 25, line 27 to page 27, line 6), as well as Example 5 (inventive) and Comparative Example 2 of the present invention (Table 2, below, see also page 24, lines 22-30 and page 27, line 6 to page 28, line 17) indicate that a higher degree of erosion of the inner layer prior to complete dissolution of the outer layer results in better absorption of the drug.

Table 1: Compound A: dog 20 mg/body

	erosion (%)	AUC (ng.h/ml)
Example 9 (inventive)	70	5299
Comparative ex. 1	24	3969

Table 2: Acetaminophen: dog 50 mg/body

	erosion (%)	AUC (ng.h/ml)
Example 5 (inventive)	55.2	1054
Comparative ex. 2	24.8	387

The present invention demonstrates erosion of approximately 40% to approximately 90% (*e.g.*, 70% and 55.2 %). Clearly, the addition of filler in the core of the instant invention allows substantial core erosion to a solution state prior to exposure to the lower digestive tract environment.

However, there is more. In order to show that the hypothetical combination of Dandiker *et al.* and Nakashima *et al.* do not result in a core that is substantially eroded prior to erosion of an outer layer, Dr. Kondo declared that tablets were prepared according to the examples of Dandiker *et al.* and Nakashima *et al.* (see, paragraph 10, Table 3, page 4 of the

Kondo declaration). The dosage forms were prepared, and moistened in the test solution at 37°C for 3 hours, and then the gelated part of the tablet was peeled off and the uneroded core was removed. The core was dried in a dryer overnight at 40°C and then weighed. The percentage erosion of the core tablet was calculated from the dry weight and initial weight.

As Dr. Kondo declares in Paragraph 11, the tablet using the core and outer layer of Dandiker *et al.* (Formulation 1 in Table 3) showed no erosion at all (last entry) of the core prior to complete erosion of the outer layer. In addition, the tablets using the core of Dandiker *et al.* and an outer layer comprising the formulation of Nakashima *et al.* (Formulations 2 and 3 of Table 3) exhibited less than 5% erosion (last entry).

In stark contrast, tablets of the instant invention were formulated using the example in Test Example 3 of Comparative Example 2 of the instant invention. In contrast to the formulations of Dandiker *et al.* and Nakashima *et al.*, formulations of the instant invention demonstrate high degrees of erosion of the core prior to erosion of the outer layer (see, Tables 4 and 5, paragraph 12.).

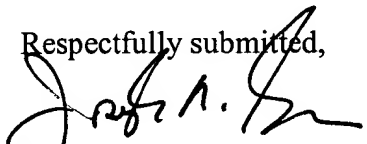
Thus, the time-released compression-coated tablets as presently claimed produce unexpectedly improved properties such that when the outer layer is finally peeled away, the inner layer is substantially dissolved. Thus, when the outer layer completely dissolves, the inner layer is already substantially dissolved and enables rapid absorption of the drug. These unexpected advantageous properties represent objective evidence sufficient to rebut a *prima facie* case of obviousness. Accordingly, the Examiner is respectfully requested to withdraw the 35 U.S.C. §103(a) rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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